Childs Nerv Syst
DOI 10.1007/s00381-016-3289-6

CASE REPORT

"Endovascular embolic hemispherectomy": a strategy for the initial management of catastrophic holohemispheric epilepsy in the neonate

Chima Oluigbo[1] · **Monica S. Pearl**[2,3] · **Tammy N. Tsuchida**[4] · **Taeun Chang**[4] · **Cheng-Ying Ho**[5] · **William D. Gaillard**[4]

Received: 23 September 2016 / Accepted: 20 October 2016

Abstract
Purpose Conflicting challenges abound in the management of the newborn with intractable epilepsy related to hemimegalencephaly. Early hemispherectomy to stop seizures and prevent deleterious consequences to future neurocognitive development must be weighed against the technical and anesthetic challenges of performing major hemispheric surgery in the neonate.
Methods We hereby present our experience with two neonates with hemimegalencephaly and intractable seizures who were managed using a strategy of initial minimally invasive embolization of the cerebral blood supply to the involved hemisphere.
Results Immediate significant seizure control was achieved after embolization of the cerebral blood supply to the involved hemisphere followed by delayed ipsilateral hemispheric resection at a later optimal age.
Conclusion The considerations and challenges encountered in the course of the management of these patients are discussed, and a literature review is presented.

✉ Chima Oluigbo
coluigbo@cnmc.org

[1] Department of Neurosurgery, Children's National Health System, 111 Michigan Avenue NW, Washington, DC, USA

[2] Department of Radiology, Children's National Health System, Washington, DC, USA

[3] Division of Interventional Neuroradiology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

[4] Department of Neurology, Children's National Health System, Washington, DC, USA

[5] Department of Neuropathology, Children's National Health System, Washington, DC, USA

Keywords Hemimegalencephaly · Endovascular embolization · Cerebral hemispheric infarction · Neonates · Epilepsy

Introduction

The management of the newborn with intractable epilepsy related to hemimegalencephaly presents multiple challenges. Uncontrolled seizures of the developing brain have deleterious implications for future neurocognitive development [11]. The multiple medications employed in the attempt to reduce seizure frequency in these patients may be accompanied by significant side effects. For example, in situations where benzodiazepine infusions are employed, the patient may require a prolonged period of intubation with its attendant risks and challenges. In addition, many commonly used antiepileptic medications have been linked to drug-induced neuronal and white matter apoptosis in the developing rodent brain [9]. In the face of medical intractability, anatomical or functional hemispherectomy is an established surgical treatment option [8].

However, early hemispherectomy in the neonate presents significant surgical challenges. The amount of intraoperative blood loss in these surgeries as a proportion of the entire blood volume of a neonate is significant. Precipitous blood loss may occur during the surgery, especially during anatomical hemispherectomy [4, 5, 7]. Intraoperative and perioperative deaths have been reported in these situations due to significant blood loss resulting in exsanguination or coagulative dysfunction resulting from massive blood transfusions along with anesthetic complications [1, 2]. In view of these challenges, many neurosurgeons defer the surgery to allow maturation of the child in terms of weight and age. The optimal criteria in terms of weight and age have not been prospectively determined, but most neurosurgeons would not perform an anatomical

Published online: 29 October 2016

hemispherectomy in a patient below 6 weeks of age or who weighs less than 10 kg.

Confronted with the afore-described conundrum in two neonates with hemimegalencephaly and intractable seizures, our team effected a strategy for initial minimally invasive embolization of the cerebral blood supply to the involved hemisphere for immediate significant seizure control followed by delayed ipsilateral hemispheric resection at a later optimal age. We hereby present our experience with the two sentinel patients who were managed using this strategy. The considerations and challenges encountered in the course of the management of these patients are discussed, and a literature review is presented.

Case reports

Case 1 (JG)

JG is a male who was born at 38-week and 5-day gestation by vaginal delivery. At 19 h of life, he began experiencing intractable seizures characterized by gaze deviation to the right, eye blinking, lip smacking, and bilateral upper extremity tonic movements. Phenobarbital was loaded at the delivery hospital with cessation of clinical seizure activity. A brain magnetic resonance imaging (MRI) scan was obtained, which showed features of left hemimegalencephaly: pachygyria and band heteropia involving the left frontal, parietal, occipital, and temporal lobes (Fig. 1). JG was transferred on the second day of life to our center for further management.

Continuous video EEG recording was initiated shortly after arrival demonstrating multiple seizures per hour in the left hemisphere. Despite the addition of fosphenytoin, JG proceeded into electrographic status epilepticus the same day. A midazolam drip reduced seizures to under ten per hour. Given the underlying dysplasia, rapid oral titration of topiramate, oxcarbazepine, and clobazam and intravenous administration of levetiracetam and lacosamide were attempted over the next 2 weeks with minimal success and continued dependency on 0.12 mg/kg/h of midazolam drip.

In multidisciplinary discussions about his management, concerns about the deleterious effects of uncontrolled seizures on his neurocognitive outcome were raised. Although anatomical hemispherectomy was the proposed definite procedure for control of his seizures, concerns about the surgical challenge and risk of significant blood loss relative to entire blood volume in this neonate mandated that the timing of this procedure be delayed. While awaiting this definite procedure, the option of embolization of the left cerebral vasculature with subsequent left hemispheric infarct and cessation of the left hemispheric seizures was discussed at the Multidisciplinary Epilepsy case conference, and then, with his parents, an informed consent was obtained.

At 22 days of life, the patient underwent staged embolization of the left cerebral vasculature. The first procedure was

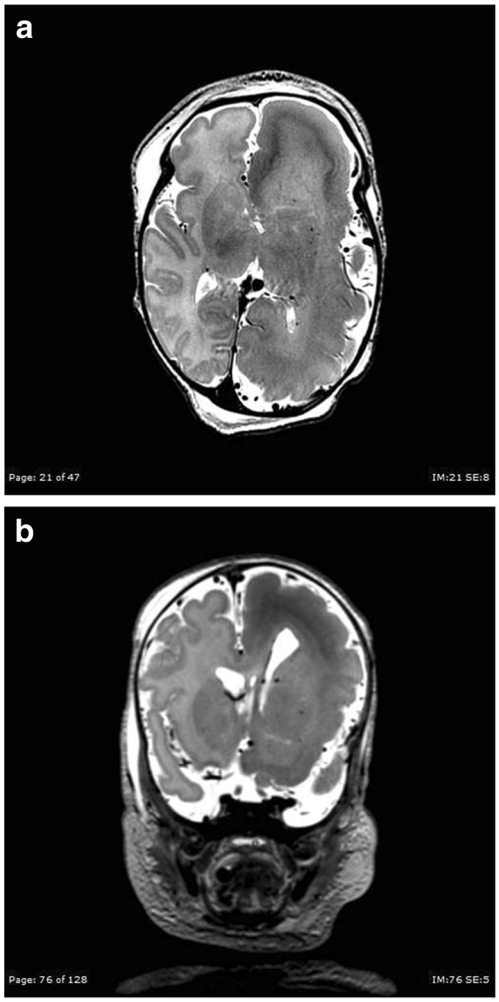

Fig. 1 **a**, **b** Axial and coronal T2W brain MRI scans of case 1 showing left hemimegalencephaly with evidence of pachygyria and band heteropia involving the left frontal, parietal, occipital, and temporal lobes

for embolization of the left middle cerebral artery as the central temporal region was the most active seizure focus (Fig. 2). Because of concerns for potential midline or uncal herniation with cerebral swelling accompanying the expected left middle cerebral artery (MCA) territory infarct, a dose of decadron prior to the procedure and a mild hypothermia protocol of 35 °C were instituted during the procedure and for 72 h afterward. Postprocedure brain MRI scan confirmed infarction of the left MCA territory (Fig. 3). This postprocedural brain MRI scan also showed that there was no evidence of excessive postprocedural brain swelling or suggestion of midline shift. After an initial increase in seizures treated with midazolam boluses and slight titration in drip rate, seizures stopped for 24 h on postop day 5. Immediately after the procedure, reduced left hemispheric epileptiform activity was noted on continuous EEG monitoring. However, subsequently, the midazolam drip was weaned to 0.04 mg/kg/h over the next 72 h with occasional left occipital and left frontopolar seizures, corresponding to the territories supplied by the left

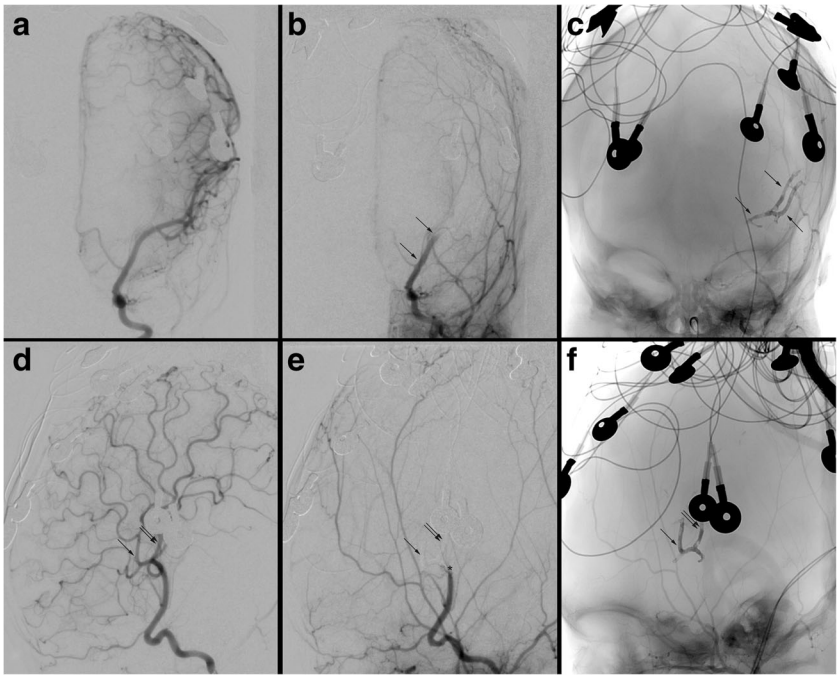

Fig. 2 Multiple AP and lateral views of a left carotid artery angiogram before and after stage 1 left MCA embolization. AP (**a**) and lateral (**d**) views demonstrate a hypoplastic left A1 segment and elongated courses of the proximal A1 and M1 segments. The superior (*single arrow* in **d**) and inferior (*double arrows* in **d**) divisions of the left MCA are demarcated on the lateral view (**d**). AP (**b**) and lateral (**e**) views after embolization show occlusion of the distal M1 segment (*asterisk* in **e**). The proximal left M1 segment (*arrows* in **b**), A1 segment, lenticulostriate arteries, and distal ICA remain patent. Unsubtracted AP (**c**) and lateral (**f**) views show the glue cast in the distal left M1 segment and proximal superior (*single arrow* in **e**, **f**) and inferior (*double arrows* in **e**, **f**) divisions of the left MCA

posterior cerebral artery (PCA) and left anterior cerebral artery (ACA), respectively.

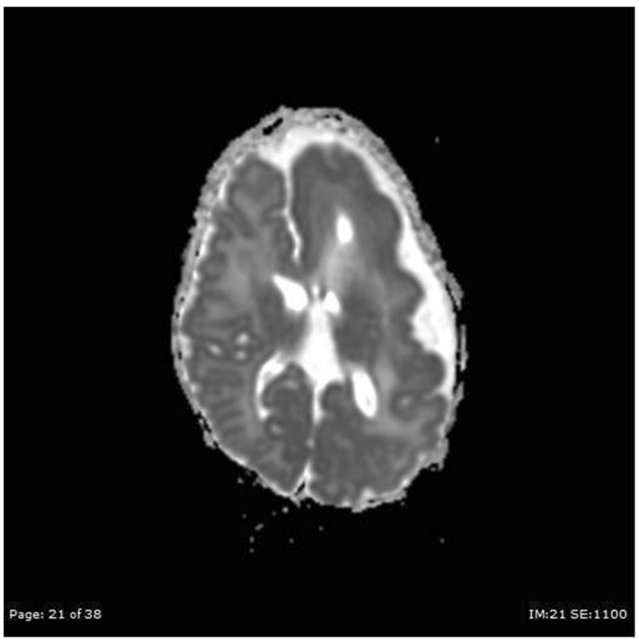

Fig. 3 ADC map of brain MRI scan showing area of restricted diffusion in left middle cerebral artery (MCA) vascular territory consistent with infarction. The limitation in the extent of infarction may have been related to the use of cooling

Therefore, at 8 weeks of age, he underwent a second embolization procedure for embolization of the left PCA and at 9 weeks of age the third and final procedure for embolization of the ACA, a small residual left MCA branch, and the posterior temporal branch of the left PCA. Postprocedural angiographic imaging confirmed that the only remaining vascular supply to the left cerebral hemisphere was to the basal ganglia (Fig. 4). After the completion of the left hemispheric embolization procedure, there was attenuation of the left hemispheric activity and cessation of the left-sided spike and wave periodic that had been seen pre-embolization. Epileptiform discharge cessation correlated with embolization of particular arteries. In the first few hours after embolization, there were a few electrographic seizures from the T3 electrode and occasional O1 seizures associated with right hemisphere slowing, but these seizures were lower in amplitude compared to prior postembolization seizures. Following this procedure, EEG showed intermittent brief seizure activity and improved spike-wave patterns seen in comparison with pre-embolization reads (Fig. 5a, b). His midazolam infusion was weaned to trace amounts, and he was subsequently extubated.

At the age of 4 months, he underwent left anatomical hemispherectomy. Intraoperative findings were of leptomeningeal attempts at revascularization via the dura as well as thickened vascular skull bone, suggesting attempts at revacularization using external carotid vascular channels. This resulted in significant bleeding and a brief period of hemodynamic instability at the

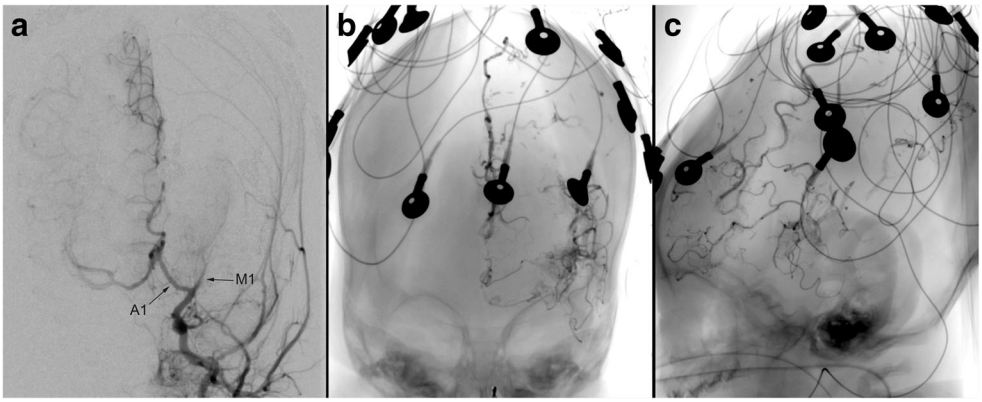

Fig. 4 AP and lateral views after embolization of the left MCA, ACA, and PCA. AP view from a left common carotid artery angiogram (**a**) shows a patent distal ICA, A1 segment, M1 segment, and lenticulostriate arteries supplying the left basal ganglia. There is opacification of the right ACA territory via a patent anterior communicating artery. Faint opacification of the right MCA territory is also seen, with inflow of unopacified blood from the patent right carotid artery. Unsubtracted AP (**b**) and lateral (**c**) views demonstrate the extensive glue cast after multiple staged embolizations

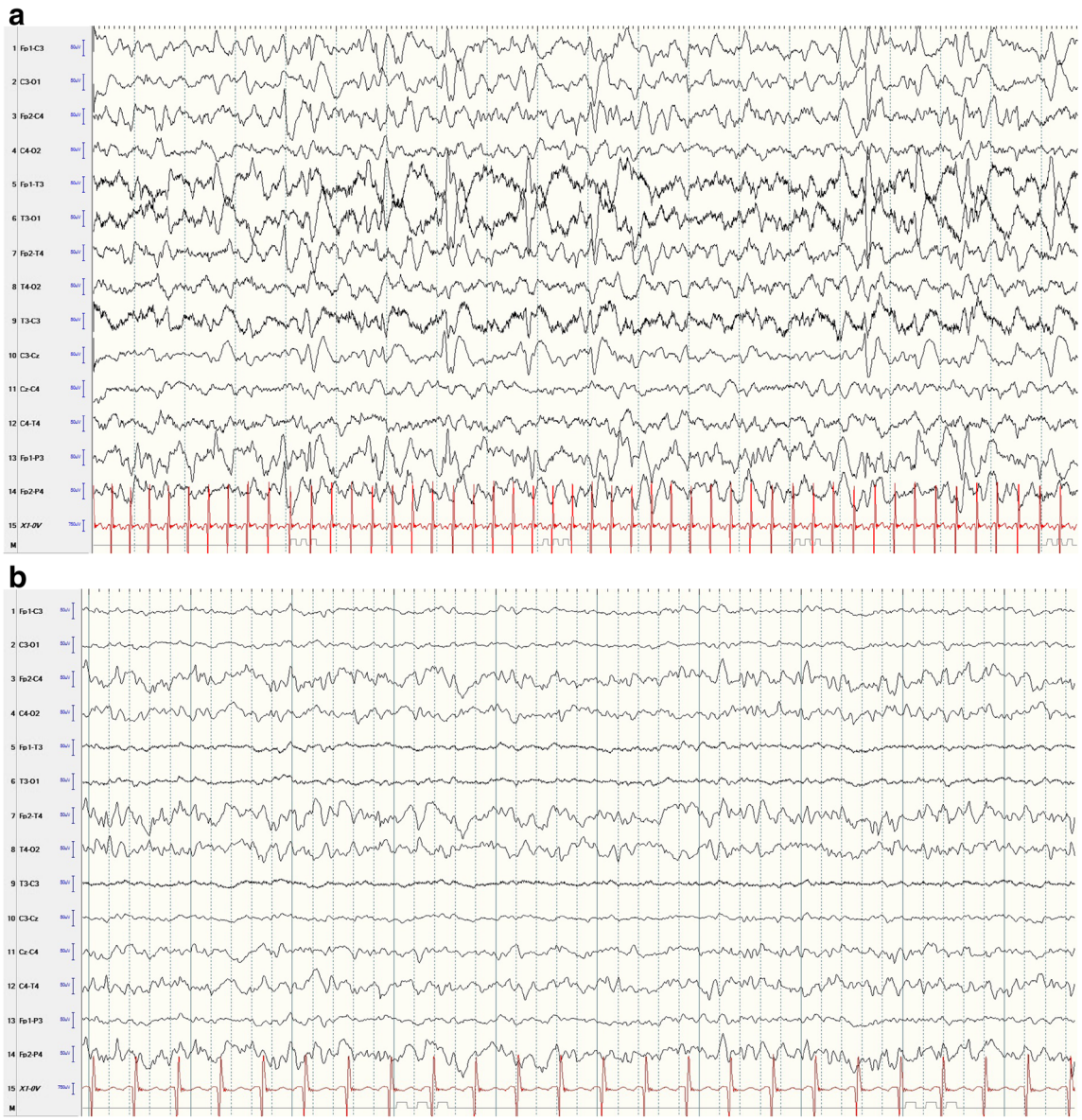

Fig. 5 **a** Pre-embolization EEG of case 1. **b** Postembolization EEG of case 1

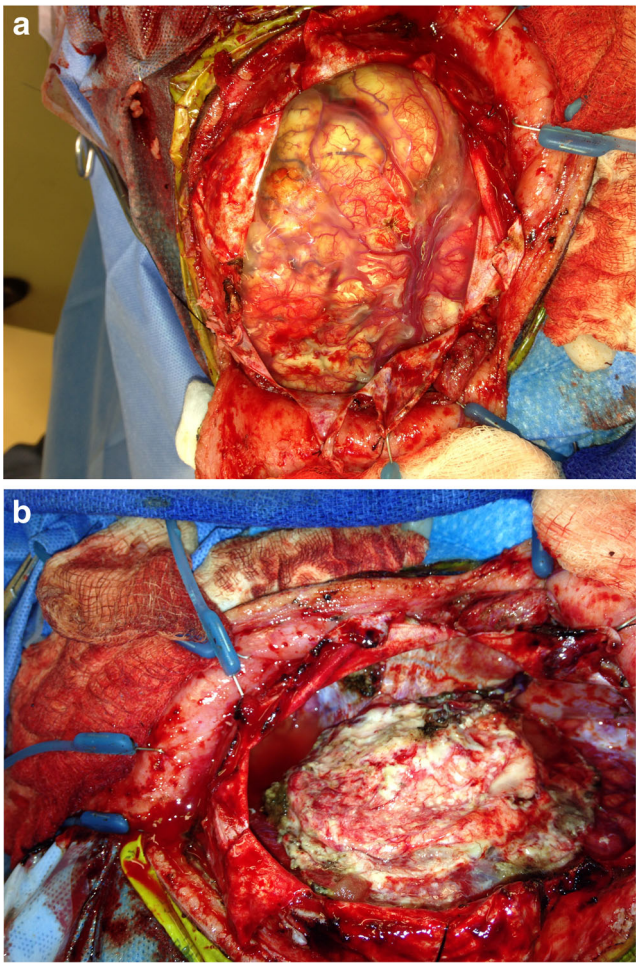

Fig. 6 **a** Intraoperative picture of case 1 showing infarcted left hemisphere. Note the embolic material in the branches of the left MCA. **b** Intraoperative picture of case 1 following completion of left anatomical hemispherectomy

stage of fashioning the craniotomy related to the bony and dural bleeding. However, the actual hemispherectomy procedure was virtually bloodless and the brain had evidence of extensive liquefactive necrosis, which was easily aspirated, and this aspect of the surgery was completed within 2 h (Fig. 6a, b). There was little by way of venous bleeding at the level of the draining veins. This may be a reflection of the fact that arterial supply to the brain had been interrupted with consequent reduction in venous outflow. Subsequent histopathological assessment of the resected brain demonstrated greatly thickened cerebral cortex with an additional layer of cytomegalic dysmorphic neurons identified in the subcortical white matter. Scattered microcalcifications were present in the cortex. Background brain tissue showed prominent coagulative necrosis, cavitary changes, gliosis, and macrophage infiltrates, consistent with cerebral infarction (Fig. 7a, d).

Following surgery, he remained seizure free, his midazolam drip was discontinued, and he was discharged home on phenobarbital, topiramate, oxcarbazepine, and lacosamide. At 25 months of age, JG remains seizure free on topiramate,

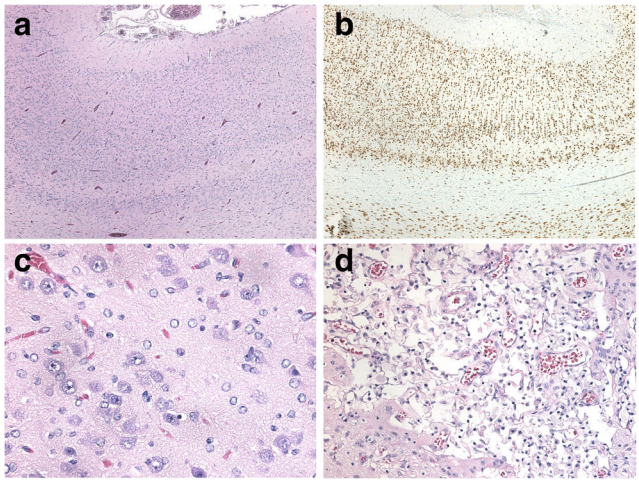

Fig. 7 **a**–**d** Histopathological slide from case 1 showing greatly thickened cerebral cortex with an additional layer of cytomegalic dysmorphic neurons identified in the subcortical white matter (indicated by *arrows*). **a** H&E stain, ×40 magnification. **b** NeuN immunohistochemical stain, ×40 magnification. **c** Neurons in the subcortical white matter layer are cytomegalic and dysmorphic, ×400 magnification. **d** Findings of cavitary changes, macrophage infiltrates, and vascular proliferation are consistent with embolization-induced brain infarction, ×200

oxcarbazepine, and clobazam. He has moderate right-sided weakness, has left gaze preference, and has a gastrostomy tube in place.

Case 2 (SM)

SM is an ex-34-week preemie female who developed medically refractory seizures on the fourth day of life, is born at 34-week and 5-day gestation without difficulty, and developed seizures at 4 days of life. She was treated with phenobarbital and levetiracetam. When a follow-up routine EEG captured subclinical seizures, SM was transferred to our center for further management. Brain MR imaging showed left hemimegalencephaly as well as a dysplastic corpus callosum and left cerebellum with dysplastic corpus callosum, vermis, and left cerebellum (Fig. 8). Repeated EEGs showed subclinical status epilepticus. Continuous video EEG recording was significant for electrodecrements and persistent large left hemisphere sharp and wave activity.

Following extensive discussions with her family and informed consent, she underwent multistaged endovascular embolization procedures of her left cerebral vascular supply starting with left MCA embolization at 8 weeks of life (postnatal age 43 weeks) and final selective embolization of the left ACA at the A2-A3 junction at 9 weeks of life (postnatal age 44 weeks). However, residual supply to the left inferior frontal lobe was from A2 branches from the right ACA. In order to avoid risks to her remaining functional circulation, embolization of the right ACA contributors to the left inferior frontal

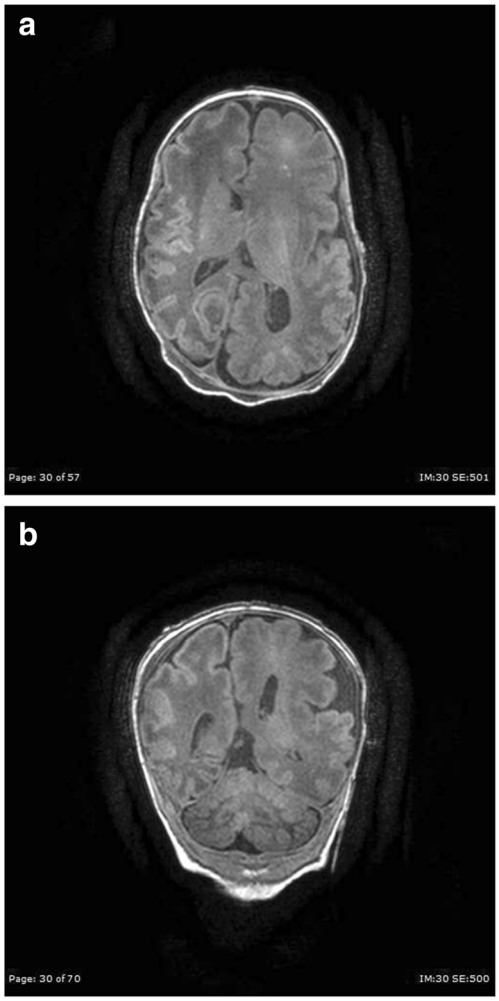

Fig. 8 **a**, **b** Axial and coronal T1W brain MRI scan of case 2 showing left hemimegalencephaly as well as dysplastic left cerebellum

lobe was not performed. Her EEG continued to show frequent large left frontal spike and wave discharges in an otherwise suppressed left hemisphere despite phenobarbital, levetiracetam, oxcarbazepine, topiramate, and fosphenytoin treatments. Therefore, we proceeded to a left anatomical hemispherectomy at 18 weeks of life (postnatal age 52 weeks). Her postoperative recovery was unremarkable and without seizure activity. A follow-up EEG recording on postoperative day 5 revealed left hemisphere slowing with absence of any epileptiform discharges.

At 23 months of age, SM remains seizure free since her hemispherectomy on phenobarbital, levetiracetam, and oxcarbazepine. She is gastric tube feeding dependent due to oral aversion and has moderate right hemiparesis.

Discussion

Endovascular embolization is routinely used for the targeted treatment of arteriovenous malformations and vascular brain tumors. However, the intentional endovascular embolization of the entire vascular supply of a brain hemisphere is distinctly unusual. The expected outcome of such an endeavor would be the infarction of the corresponding hemisphere and loss of cortical output.

Mathis et al. published their experience on their treatment of intractable epilepsy in a case of hemimegalencephaly using preoperative hemispheric embolization [10]. In this case, a 17-day-old neonate with hemimegalencephaly developed intractable epilepsy. Since the seizures remained intractable to medications, their neurosurgical team considered progressing to hemipherectomy but requested staged cerebral hemispheric embolization to minimize blood loss (not primarily to disrupt the seizure activity). However, following the embolization, the patient remained seizure free until the age of 14 months when her clinical seizure activity recurred at which point she underwent anatomical hemispherectomy.

In our case, the primary objective of hemispheric endovascular embolization was disruption of cortical epileptiform activity. A secondary objective was the minimization of blood loss at the time of eventual hemispherectomy. These objectives were achieved. With creation of a hemispheric stroke, we were able to achieve significant seizure control in both cases following complete hemispheric vascular occlusion. Surgery could be delayed in these patients, and intraoperative blood loss was minimized at the time of anatomical hemispherectomy.

There is no direct clinical evidence that the intentional infarction of a brain hemisphere will disrupt epileptiform cortical activity. However, there is preclinical evidence. Wiederholt studied the acute and chronic effects of unilateral cerebral infarction on the EEG of rats [12]. He observed that following experimental unilateral ligation of the common and external carotid arteries in experimental rats, they developed ipsilateral attenuation of EEG activity. We observed this on continuous EEG monitoring during the embolization procedure in case 1. After the completion of the left hemispheric embolization procedure, there was attenuation of the left hemispheric activity and cessation of the persistent left-sided spike and wave activity that was seen pre-embolization. Epileptiform discharge cessation correlated with the vascular territory that was embolized. Postembolization EEG showed minimal seizure activity and improved spike-wave patterns seen in comparison with pre-embolization reads. This is, to the best of our knowledge, the first clinical description of real-time EEG changes during intentional complete hemispheric vascular occlusion.

In both patients, we staged the embolizations to avoid complications related to postischemic brain swelling, mass effect, and intracranial hypertension [6]. This is especially important in neonates with hemimegalencephaly. This practice was also recommended in the paper by Mathis et al. [10]. We do not think that the hypothermia protocol adopted in case 1 played a

significant role in controlling the brain swelling. The use of staged embolization appears to be a more useful strategy.

An interesting intraoperative finding during the anatomical hemispherectomy surgical procedures was increased calvarial vascularity and attempts at leptomeningeal collateral revascularization with the dura using external carotid vascular channels. In fact, in patient 1, this contributed to significant bleeding and a brief period of hemodynamic instability at the stage of fashioning the craniotomy related to the bony and dural bleeding. However, the actual hemispherectomy procedure was virtually bloodless and the brain had evidence of extensive liquefactive necrosis, which was easily aspirated, and this aspect of the surgery was completed within 2 h. It is, therefore, important that the surgeon and anesthesiologist anticipate and plan for this likelihood of more than normal bony and dural bleeding at the early phases of the surgery. It is interesting to note that in rat experiments, Wiederholt noted that simply ligating the common carotid artery alone led to only transient attenuation of the ipsilateral EEG activity, which then reversed after a few days and he attributed this to significant collateral blood flow through the external carotid artery branches. However, they noted improved predictability of cerebral infarction and attenuation of ipsilateral EEG activity by ligating the common and the external carotid arteries, which significantly reduced this collateral blood flow [12]. The increased calvarial and leptomeningeal vascularity seen in our patients likely represents similar attempts at collateral revascularization using external carotid vascular channels.

Hydrocephalus is a well-documented risk following hemispherectomy and occurs in up to 20–30 % of patients [3]. None of our patients that underwent this embolization procedure has developed hydrocephalus after 2 years of follow-up. However, the small number of patients and the relatively short duration of follow-up make it difficult to determine if embolization increases or diminishes this risk of hydrocephalus.

Finally, while we found this technique to be very helpful in the situation described, we certainly do not recommend it in all cases. As in established practice, every attempt should be made to establish seizure control by medical means before resorting to invasive or surgical therapy. This technique is primarily directed at controlling intractable seizures in the neonate who is too young (or medically unstable) to undergo hemispherectomy and who has failed medical treatment. However, we would not recommend this procedure as a first line of treatment especially in infants whose seizures are partially controlled by medical treatment. Functional hemispherectomy which involves hemispheric disconnection is associated with significantly decreased blood loss compared to anatomical hemispherectomy and is the preferred technique for hemispherectomy in early life. However, functional hemispherectomy is challenging in patients with hemimegalencephaly whose anatomical landmarks are distorted. It is also associated with reduced seizure control outcomes compared to anatomical hemispherectomy in patients with hemimegalencephaly [7]. Thus, this technique of initial "endovascular embolic hemispherectomy" may be best suited for the neonate with medically refractory epilepsy related to hemimegalencephaly, a situation which we encountered in both of our patients.

Compliance with ethical standards

Conflict of interest The authors of this paper do not have any conflict of interest to declare.

References

1. Carson BS, Javedan SP, Freeman JM et al (1996) Hemispherectomy: a hemidecortication approach and review of 52 cases. J Neurosurg 84: 903–911
2. Cook SW, Nguyen ST, Hu B et al (2004) Cerebral hemispherectomy in pediatric patients with epilepsy: comparison of three techniques by pathological substrate in 115 patients. J Neurosurg 100: 125–141
3. Di Rocco C, Iannelli A (2000) Hemimegalencephaly and intractable epilepsy: complications of hemispherectomy and their correlations with the surgical technique. A report on 15 cases. Pediatr Neurosurg 33:198–207
4. Di Rocco C, Battaglia D, Pietrini D et al (2006) Hemimegalencephaly: clinical implications and surgical treatment. Childs Nerv Syst 22: 852–866
5. Dorfer C, Ochi A, Snead OC 3rd et al (2015) Functional hemispherectomy for catastrophic epilepsy in very young infants: technical considerations and complication avoidance. Childs Nerv Syst 31: 2103–2109
6. Frank JI (1995) Large hemispheric infarction, deterioration, and intracranial pressure. Neurology 45:1286–1290
7. Gonzalez-Martinez JA, Gupta A, Kotagal P et al (2005) Hemispherectomy for catastrophic epilepsy in infants. Epilepsia 46:1518–1525
8. Honda R, Kaido T, Sugai K et al (2013) Long-term developmental outcome after early hemispherotomy for hemimegalencephaly in infants with epileptic encephalopathy. Epilepsy Behav 29:30–35
9. Kaushal S, Tamer Z, Opoku F et al (2016) Anticonvulsant drug-induced cell death in the developing white matter of the rodent brain. Epilepsia
10. Mathis JM, Barr JD, Albright AL et al (1995) Hemimegalencephaly and intractable epilepsy treated with embolic hemispherectomy. AJNR Am J Neuroradiol 16:1076–1079
11. Roulet-Perez E, Davidoff V, Mayor-Dubois C et al (2010) Impact of severe epilepsy on development: recovery potential after successful early epilepsy surgery. Epilepsia 51:1266–1276
12. Wiederhold WC, Pariser SF (1974) Acute and chronic effects of unilateral cerebral infarction on the EEG and behavior of the rat. Stroke 5:85–91